UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/047,855	01/15/2002	Lillian Wei-Ming Chiang	MPI00-557P1RM	5102

30405 7590 08/10/2005

MILLENNIUM PHARMACEUTICALS, INC.
40 Landsdowne Street
CAMBRIDGE, MA 02139

EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/047,855	CHIANG, LILLIAN WEI-MING	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/15/02, 6/4/03, 6/8/05*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5-0-0

DETAILED ACTION

1. The Election filed June 8, 2005 in response to the Office Action of April 6, 2005 is acknowledged and has been entered. Applicants elected Group XVI (claim 23) without traverse. Applicants cancelled claims 1-23 and added claims 24-33 drawn to the invention of claim 23. Claims 24-33 are currently under prosecution.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. The term "**modulate**" in claims 24 and 29 is a relative term which renders the claim indefinite (24a, 24b, 29a, and 29b). The term "**modulate**" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

3. Claims 24-33 are indefinite because claims 24 and 29 recite the phrase "**modulating apoptosis**." This renders the claim indefinite because the phrase **"modulating apoptosis"** is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification

suggests some examples of compounds capable of modifying apoptosis, or "modulators" (p. 56, lines 1-6) that bind programmed cell death-related polypeptides or have a stimulatory or inhibitory effect on their expression or activity, however, it is unclear what the limitations of "modulating apoptosis" are because the specification does not define said compound. Given the above reasons, the metes and bounds of the claims cannot be determined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 24-28 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation wherein "a polypeptide which is encoded by a nucleic acid molecule **comprising** a nucleotide sequence which is **at least 95% identical to** a nucleic acid comprising the nucleotide sequence of SEQ ID NO:4" and "an amino acid sequence which is **at least 95% identical to** the amino acid sequence of SEQ ID NO:3" has no clear support in the specification and the claims as originally filed. THIS IS A NEW MATTER REJECTION.

Applicant points to page 4, lines 16-20, and 30; page 5, lines 23-27; page 12, lines 13-24; page 19, line 19-page 20, line 4; page 56, lines 2-6; page 58, lines 11-16; page 85, line 16; and page 86, line 10- page 87, line 2 to support the newly added claim

limitation. However, a review of page 4, lines 16-20, and 30 reveals support for "antibodies and antibody fragments that selectively bind the programmed cell death-related polypeptides and fragments." A review of page 5, lines 23-27 reveals support for "a method for identifying a compound that binds to or modulates the activity of a programmed cell death-related polypeptide." A review of page 12, lines 13-24 reveals support for "programmed cell death in rat cerebellar granule neurons induced by potassium withdraw dependent on *de novo* RNA synthesis." A review of page 19, line 19-page 20, line 4 reveals support for examples of NARC 16 activity and methods of assaying cell cycle progression. A review of page 56, lines 2-6 reveals support for identifying modulators. A review of page 58, lines 11-16 reveals support for determining the ability of a test compound to modulate the activity of a programmed cell death-related polypeptide. A review of page 85, line 16 reveals support for a second, brain-restricted isoform of NARC 16. Finally, a review of page 86, line 10- page 87, line 2 reveals support for an example of programmed cell death induced in cerebellar granule neurons by NARC 10 and NARC 16.

The cited support has been considered but has not been found persuasive because the cited support is not drawn to an assay of a polypeptide which is encoded by a nucleic acid molecule comprising a nucleotide sequence which is **at least 95% identical to** a nucleic acid comprising the nucleotide sequence of SEQ ID NO:4 and an amino acid sequence which is **at least 95% identical to** the amino acid sequence of SEQ ID NO:3. Although the specification teaches a method for identifying a compound capable of modulating apoptosis comprising a polypeptide which is encoded by a

nucleic acid molecule comprising SEQ ID NO:4 and an amino acid sequence comprising SEQ ID NO:3, the specification neither states nor demonstrates a method for identifying a compound capable of modulating apoptosis comprising a polypeptide which is encoded by a nucleic acid molecule comprising a nucleotide sequence which is **at least 95% identical** to SEQ ID NO:4, and an amino acid sequence which is **at least 95% identical** to SEQ ID NO:3. The subject matter claimed in claims 24-28 narrows the scope of the invention as originally disclosed in the specification.

5. Claims 24-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the **written description** requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth the polypeptide encoded by a nucleic acid consisting of SEQ ID NO:4 and an amino acid sequence consisting of amino acid sequence SEQ ID NO:3, therefore the written description is not commensurate in scope with the claims drawn to a multitude of nucleotides or polypeptides with **at least 95% identity** to SEQ ID NO:4 and SEQ ID NO: 3, respectively. THIS IS A WRITTEN DESCRIPTION REJECTION.

The claims are drawn to a method for identifying a compound capable of modulating apoptosis comprising a polypeptide which is encoded by a nucleic acid molecule **comprising** a nucleotide sequence which is **at least 95%** identical to a nucleic acid comprising SEQ ID NO: 4 and an amino acid sequence which is **at least**

95% identical to SEQ ID NO: 3. The specification only discloses the nucleotide sequence SEQ ID NO: 4 and amino acid sequence SEQ ID NO: 3 (p. 21, lines 13-14). The specification does not disclose any other sequences which are at least 95% identical to SEQ ID NO: 3 and 4 or any other sequences comprising SEQ ID NO: 3 and 4 as broadly encompassed in the claims.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factors present in the claim are recitations of "a nucleic acid molecule **comprising** a nucleotide sequence which is **at least 95% identical to"** SEQ ID NO:4 or an amino acid sequence which is **"at least 95% identical to"** SEQ ID NO:3. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The

court stated that " [a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name', of the claimed subject matter sufficient to distinguish it from other materials. " Id. At 1567, 43 USPQ2d at 1405. The court also stated that:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-

Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of the sequences which are at least 95% identical to SEQ ID NO:3 and 4 that could be successfully used in the claimed invention, per Lilly by structurally describing representative sequences or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not directly describe sequences which are at least 95% identical to SEQ ID NO:3 and 4 that will function as claimed in a manner that satisfies either the Lilly or Enzo standards. Although the specification discloses SEQ ID NO:3 and 4, this does not provide a description of the broadly claimed sequences which are at least 95% identical to SEQ ID NO:3 and 4 that would satisfy the standard set out in Enzo because the specification provides no functional characterisitics coupled to structural features.

Further, the specification also fails to describe sequences which are at least 95% identical to SEQ ID NO:3 and 4 by the test set out in Lilly because the specification describes only SEQ ID NO:3 and 4. Therefore it necessarily fails to describe a representative number of such species.

Thus, the specification does not provide an adequate written description of the sequences at least 95% identical to SEQ ID NO:3 and 4 which will function as claimed in the claimed method of identifying compounds capable of modulating apoptosis required to practice the claimed invention. Since the specification fails to adequately describe the sequences at least 95% identical to SEQ ID NO:3 and 4, it also fails to adequately describe the method.

Note: If applicant were to overcome the preceding rejection (s) under 35 U.S.C. 112, first paragraph, the following claims would still be rejected under 35 U.S.C. 112, first paragraph, scope of enablement:

6. Claims 24-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a compound capable of modulating apoptosis comprising a polypeptide encoded by a nucleic acid molecule comprising SEQ ID NO:4 and an amino acid sequence comprising SEQ ID NO:3, does not reasonably provide enablement for a method for identifying a compound capable of modulating apoptosis comprising a polypeptide which is encoded by a nucleic acid molecule **comprising** a nucleotide sequence which is **at least 95%** identical to a nucleic acid comprising SEQ ID NO: 4 and an amino acid sequence which is **at least 95%** identical to SEQ ID NO: 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are drawn to a method for identifying a compound capable of modulating apoptosis comprising a polypeptide which is encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleic acid comprising SEQ ID NO: 4 and an amino acid sequence which is at least 95% identical to SEQ ID NO: 3. This means the claims are drawn to a broad spectrum of sequences which are at least 95% identical to SEQ ID NO:3 and 4.

The specification teaches a method for identifying a compound capable of modulating apoptosis comprising combining a test compound with a sample comprising a polypeptide consisting of SEQ ID NO:3 and polypeptide encoded by SEQ ID NO:4 (p. 14, lines 9-12, and p. 59, line 26 - p. 60, line 8).

One cannot extrapolate the teaching of the specification to the scope of the claims because the claims as written are drawn to sequences which are 95% identical to SEQ ID NO:3 and 4. Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape of a protein and determines the ability of said protein to fold into unique three-dimensional structures that allows them to function. Bowie et al further teach that certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (p. 1306, cols 1 and 2). Clearly, the three dimensional structure of a protein is critical to its function, particularly relating to the glycerophosphoryl phosphodiester phosphodiesterase activity of the polypeptide encoded by SEQ ID NO:3 and 4 and the ability of a test compound to modulate its activity. However, neither the specification nor the art of record provide teachings that provide information about the sequences which are 95% identical to SEQ ID NO:3 and 4 required for the method for identifying a compound capable of modulating apoptosis. This information appears to be critical because the art recognizes (see Bowie et al above) that it is the protein sequence that determines the three dimensional shape of a protein and suggests that the three-dimensional structure of the protein molecule may be essential for the protein's function and ability to be modulated. Thus, in the absence of guidance in the specification, the effects of the undefined sequences which are 95% identical to SEQ ID NO:3 and 4, cannot be predicted and one could not determine how to practice the claimed invention or predict which of the

whole universe of broadly claimed polypeptides would function as claimed with a reasonable expectation of success.

Therefore, one of skill in the art would be subject to undue experimentation to practice the method for identifying a compound capable of modulating apoptosis comprising a polypeptide encoded by a sequence which is 95% identical to SEQ ID NO:3 and 4. One of skill in the art would not be able to anticipate what polypeptides would allow one to identify compounds capable of modulating apoptosis. Given the lack of guidance in the specification and the unpredictability in the art, one of skill in the art would be subject to undue experimentation in order to practice the claimed invention.

7. Claims 29, 30 and 33 are rejected and if applicant were able to overcome the rejection as set forth above, claims 24, 25 and 28 will still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a compound capable of modulating apoptosis comprising a sample wherein the sample comprises a **brain cell or neuron** expressing the polypeptide, does not reasonably provide enablement for a method for identifying a compound capable of modulating apoptosis comprising a sample wherein the sample comprises a cell expressing the polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are drawn to method for identifying a compound capable of modulating apoptosis comprising a sample wherein the sample comprises a cell

expressing the polypeptide. This means the claims are drawn to a sample comprising **any** cell expressing the polypeptide. The specification discloses the expression of the polypeptide in cerebellar granule neurons that induces apoptosis (Example 2) and an isoform of NARC 16 that is brain-restricted (particularly in Example 1, p. 85, lines 16-17).

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to any and all cells, and applicant has not enabled all of these types of cells because it has not been shown that all cells are capable of expressing a polypeptide encoded by SEQ ID NO:3 and 4 and are capable of functioning as that which is being disclosed. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be reasonably predicted that any and all cells will predictably function as disclosed. Given the undefined nature of the broadly claimed group of cells, it is not clear that one would be able to identify a compound capable of modulating apoptosis comprising a sample wherein the sample comprises any cell expressing the polypeptide based only on the information in the specification, particularly if the cell does not express the polypeptide externally or cannot induce apoptosis as a result of expressing the polypeptide. The specification provides insufficient guidance with regard to this issue and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the claimed invention of a method for identifying a compound capable of modulating apoptosis would function as broadly claimed with a reasonable expectation of success.

For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

8. Claims 24-33 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation wherein the method comprises "combining the compound selected with **a cell** expressing the polypeptide (claims 24 and 29)," "determining the effect of the compound on apoptosis of the **cell** (claims 24 and 29)," and "wherein the sample comprises **a cell** expressing the polypeptide (claims 25 and 30)" has no clear support in the specification and the claims as originally filed. The term "**cell**" reads on both *in vitro* and *in vivo*. THIS IS A NEW MATTER REJECTION.

Applicant points to page 4, lines 16-20, and 30; page 5, lines 23-27; page 12, lines 13-24; page 19, line 19-page 20, line 4; page 56, lines 2-6; page 58, lines 11-16; page 85, line 16; and page 86, line 10- page 87, line 2 to support the newly added claim limitation. However, a review of page 4, lines 16-20, and 30 reveals support for "antibodies and antibody fragments that selectively bind the programmed cell death-related polypeptides and fragments." A review of page 5, lines 23-27 reveals support for "a method for identifying a compound that binds to or modulates the activity of a programmed cell death-related polypeptide." A review of page 12, lines 13-24 reveals support for "programmed cell death in rat cerebellar granule neurons induced by potassium withdraw dependent on *de novo* RNA synthesis." A review of page 19, line 19-page 20, line 4 reveals support for examples of NARC 16 activity and methods of

assaying cell cycle progression. A review of page 56, lines 2-6 reveals support for identifying modulators. A review of page 58, lines 11-16 reveals support for determining the ability of a test compound to modulate the activity of a programmed cell death-related polypeptide. A review of page 85, line 16 reveals support for a second, brain-restricted isoform of NARC 16. Finally, a review of page 86, line 10- page 87, line 2 reveals support for an example of programmed cell death induced in cerebellar granule neurons by NARC 10 and NARC 16.

The cited support has been considered but has not been found persuasive because the cited support is not drawn to an *in vivo* assay of a polypeptide. Although the specification teaches an *in vitro* method for identifying a compound capable of modulating apoptosis comprising a cell sample (p. 59, line 26 to p. 60, line 8), the specification neither states nor demonstrates an *in vivo* method for identifying a compound capable of modulating apoptosis comprising a sample wherein the sample comprises a cell. The subject matter claimed in claims 24-33 broaden the scope of the invention as originally disclosed in the specification. This rejection may be obviated by an amendment to the claims that reads on an *in vitro* method for identifying a compound capable of modulating apoptosis.

9. Claims 24-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a compound capable of modulating apoptosis in cell culture (*in vitro*), does not reasonably provide enablement

for a method for identifying a compound capable of modulating apoptosis *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are drawn to a method for identifying a compound capable of modulating apoptosis comprising a test compound with a sample wherein the sample comprises the polypeptide (SEQ ID NO:3) or a cell expressing the polypeptide, this means the claims are broadly drawn to a method for identifying a compound capable of modulating apoptosis wherein the claimed method encompasses *in vivo* screening, because a **cell** may be broadly interpreted as being part of an *in vivo* or *in vitro* sample. The specification teaches apoptosis induced in cerebellar granule neurons by NARC 16 in cell culture (Example 2, p. 86). However, the claims are not enabled because said teachings represent insufficient guidance and objective evidence to predictably enable the use of the claimed invention. Thus, the claims are not enabled for a method for identifying a compound capable of modulating apoptosis *in vivo*. Those of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree

of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be reasonably predicted that a method for identifying a compound capable of modulating apoptosis will predictably function as disclosed. Therefore, in view of the lack of predictability of the prior art, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as broadly claimed.

Note: If applicant were to overcome the preceding rejection (s) under 35 U.S.C. 112, first paragraph, the following claims would still be rejected under 35 U.S.C. 112, first paragraph, scope of enablement:

10. Claims 24-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a compound capable of modulating apoptosis comprising combining the compound selected with a sample of cells and determining the effect of the compound on apoptosis of cells, does not reasonably provide enablement for a method for identifying a compound capable of modulating apoptosis comprising combining the compound selected with **a cell** and determining the effect of the compound on apoptosis of **the cell** (claims 24 and 29). The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are drawn to a method for identifying a compound capable of modulating apoptosis comprising combining the compound selected with **a cell** and determining the effect of the compound on apoptosis of **the cell** (claims 24 and 29), this means the claims are drawn to an assay that comprises a single cell.

The specification discloses apoptosis induced and detected in cerebellar granule neurons by NARC 16 in cell culture (Example 2, p. 86) and discloses a method of identifying modulators of apoptosis wherein "the level programmed cell death-related mRNA or protein expression in the **cells** [of the sample tested] can be determined by methods described herein for detecting programmed cell death-related mRNA or protein (p. 59, line 26 to p. 60, line 8)," meaning a sample of multiple cells was needed to detect apoptosis. However, the claims are not enabled because said teachings represent insufficient guidance and objective evidence to predictably enable the use of the claimed invention. Thus, the claims are not enabled for a method for identifying a compound capable of modulating apoptosis comprising combining the compound selected with **a cell** and determining the effect of the compound on apoptosis of **the cell**. Those of skill in the art recognize that an assay comprising a single cell or insufficient amount of cells would yield undetectable results, hence a compound capable of modulating apoptosis would not be identified by the claimed method because the level or presence of apoptosis would be undetectable.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be reasonably predicted that a method for identifying a compound capable of modulating apoptosis will predictably function as disclosed. Therefore, in view of the lack of predictability of the prior art, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as broadly claimed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Laura B Goddard, Ph.D.
Examiner
Art Unit 1642

SUSAN UNGAR, PH.D
PRIMARY EXAMINER